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Cancer incidence in a Swedish cohort with high exposure to perfluoroalkyl substances in drinking water

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ABSTRACT

Background: The use of firefighting foams at a military airport resulted in high levels of perfluorinated substances (PFAS) in the drinking water distributed to one-third of households in the Swedish municipality of Ronneby between the mid-1980s and the end of 2013.
Method: The Ronneby Register Cohort, a large cohort comprising all individuals (N = 60,507) who ever lived in the Ronneby municipality during the period of drinking water contamination, was linked to the Swedish Cancer Register 1985–2016. Individual exposure was classified based on comprehensive data on yearly residential address and water distribution. External analysis explored standardized cancer incidence ratios (SIR) for residents never, or ever, residing in the contaminated water district, compared with those residing in other towns in the same county as reference population. Cox models provided hazard ratios (HR) for different exposure groups within the cohort.
Results: 5,702 individuals with cancer were identified. SIR for overall cancer was 1.04 for men (95%CI 0.96–1.12) and 0.89 for women (95%CI 0.82–0.96) who ever lived in the contaminated drinking water area. Kidney cancer, which was reported with increased risk in C8 study, showed somewhat elevated HR in this study (HR 1.27; 95%CI 0.85–1.89). The HR was modestly elevated for bladder cancer (HR 1.32; 95%CI 1.01–1.72), and reduced for prostate cancer (HR 0.83; 95%CI 0.71–0.98). In subjects who ever lived in the contaminated water area during 2005–2013, when exposure was estimated to be highest, higher risks for kidney cancer (HR 1.84; 95%CI 1.00–3.37) but lower for prostate cancer (HR 0.76; 95%CI 0.59–0.98) were observed.
Conclusion: Analysis of this large cohort exposed to high levels of PFAS, dominated by PFHxS and PFOS, revealed no evidence for an overall increased risk of cancer. A moderately increased risk of kidney cancer was observed, in accordance with previous findings after PFAS exposure dominated by PFOA.

1. Introduction

Pollution with perfluoroalkyl substances (PFAS), a family of chemical compounds widely used in industry and consumer products, has become a global problem since PFAS are highly persistent and accumulate in the environment. Humans are exposed to PFAS from food, indoor air and dust. Additionally, pollution of drinking water from industrial production and firefighting foam can lead to substantial exposure to local populations (Guelfo and Adamson, 2018; Hu et al., 2019).

While non-malignant health effects of PFAS exposure have been investigated in epidemiological studies and recently summarized by the European Food Safety Authority (EFSA) (Knutsen and Alexander, 2018; Schrenk and Bignami, 2020), evidence on cancer risk remains scarce. The International Agency for Research on Cancer (IARC) classified the PFAS perfluorooctane acid (PFOA) as possibly carcinogenic to humans (Group 2 B) (Benbrahim-Tallaa et al., 2014). On evaluating the evidence for the carcinogenicity of PFOA in humans, the IARC found it limited and based principally on findings in the C8 Science Panel Study (Barry

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Table 1
PFAS levels in drinking water from the contaminated waterworks, the minimally contaminated waterworks, and the main waterworks in Karlshamn, a neighbouring municipality without PFAS in the drinking water.

PFAS	*Contaminated waterworks in Ronneby* (ng/L) [a,b]	*Minimally contaminated waterworks in Ronneby* (ng/L) [a,b]	*Main waterworks in Karlshamn* (ng/L) [c]
PFPeA	38	10	<0.6
PFHxA	320	3.6	<0.3
PFHpA	32	1.4	<0.3
PFOA	100	1.0	<0.3
PFBS	130	<2.6	<0.3
PFHxS	1700	4.6	<0.3
PFHpS	60	<1	<0.3
PFOS	8000	27	<0.2
Sum of PFAS [d]	10,380	47.6	<5

Note: PFAS, perfluoroalkyl substances; PFPeA, perfluoropentanoic acid; PFHxA, perfluorohexanoic acid; PFHpA, perfluoroheptanoic acid; PFOA, perfluorooctanoic acid; PFBS, perfluorobutane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFHpS, perfluoroheptane sulfonic acid; PFOS, perfluorooctane sulfonic acid.

[a] Multiple water samples were taken. These data are from water sampled on December 10, 2013, the very last sample before the contaminated waterworks was closed.

[b] PFAS analysis of drinking water was performed by a commercial water analysis company, SYNLAB (SYNLAB Analytics & Services Sweden AB, Linköping, Sweden). German standard methods were used to determine selected polyfluorinated compounds in water using liquid chromatography–tandem mass spectrometry (LC–MS/MS) after solid–liquid extraction (method designation: DIN 38407–42). SYNLAB is accredited by SWEDAC according to Swedish standard SS-EN ISO/IEC 17025.

[c] Water sampled on January 15, 2020.

[d] Sum of all PFAS with levels above the limit of detection for waterworks in Ronneby. For Karlshamn, the sum of PFAS was reported by the water analysis company.

et al., 2013; Vieira et al., 2013). Furthermore, the EFSA panel report concluded that there was as yet no evidence for a link between exposure to PFAS and cancer risk (Schrenk and Bignami, 2020). The C8 Science Panel had concluded in 2012 that there was a "probable link" between PFOA and both kidney and testicular cancers, and two more recent review including further publications, concluded that the evidence was "suggestive" of a link between PFOA and the same two cancers (Steenland et al., 2020; Steenland and Winquist, 2021). Another recent review concluded that the association between PFOA and kidney and testicular cancer is 'most likely causal' (Bartell and Vieira, 2021). One issue that was recognized by both recent reviews is the overlapping of kidney and testicular cancer cases between the two studies based on the C8 Science Panel Study. No cancer studies of general populations exposed to high levels of perfluorooctane sulfonate (PFOS) or perfluorohexane sulfonic acid (PFHxS) have yet been published. In general population settings with background PFAS exposure, there has been no consistent evidence for increased cancer risks (Bonefeld-Jorgensen et al., 2011, 2014; Eriksen et al., 2009; Hardell et al., 2014; Hurley et al., 2018; Mancini et al., 2020; Shearer et al., 2021; Tsai et al., 2020). Previous studies regarding PFAS exposure and cancer risk are summarized in the supplementary table, with a focus on studies on the general population and larger sample size (Table S1, Supplementary Information).

The objective of the current study was to investigate the risk of cancer after longstanding exposure to high levels of PFAS in drinking water dominated by PFOS and PFHxS, and to a lesser extent PFOA.

2. Material and methods

2.1. Study setting

At the end of 2013, drinking water from one of the two municipal waterworks in Ronneby, Blekinge County, Sweden, was found to be contaminated by firefighting foams used at a nearby military airfield (a map presenting the airfield, the waterworks and the location of the municipality of Ronneby can be found in Xu et al., 2021). Drinking water containing high levels of PFOS and PFHxS, and to a lesser extent PFOA, had been distributed to approximately one-third of Ronneby households since the mid-1980s (Table 1) (Xu et al., 2021). The contaminated waterworks was immediately shut down, and drinking water was instead provided from a second, minimally contaminated waterworks. Drinking water from all other municipalities in Blekinge County (represented in Table 1 by the nearby municipality of Karlshamn) contained low levels of PFAS (Table 1).

2.2. Study population

The Ronneby Register Cohort includes every individual who was ever registered as living in Ronneby municipality between 1985 and 2013. The cohort comprises 60,507 individuals, of whom 53% are men. Information on yearly registered home and work address, education level (only available from 1990 onwards), date of death and emigration from Sweden were obtained from Statistics Sweden (www.scb.se). Information on neoplasm diagnoses were retrieved from the Swedish Cancer Register (Socialstyrelsen, 2019) through linkage to the personal ID number. As is normally the case for register studies, information on lifestyle factors and health-related behaviours (e.g. smoking status) is not available in this study.

The time of entry into the cohort is defined as the first time at which a person registered as residing in Ronneby municipality between January 1, 1985 and December 31, 2013. Individuals were followed until they first received a malignant neoplasm diagnosis, or were censored, whichever came first. Censoring occurred at death, at emigration, or after the age of 85. Individuals continued to be followed if they moved from Ronneby to another part of Sweden, since all information came from nationwide registers. Follow-up was discontinued on December 31, 2016.

2.3. Exposure assessment

There was an established link between the municipal waterworks' distribution network and individuals' residential address, and therefore it is known which homes received water from the highly contaminated waterworks during the study period (1985–2013). Between 2014 and 2016, all addresses in Ronneby receiving water from the municipal supply were supplied from the minimally contaminated waterworks, whose water had low PFAS concentrations. A few addresses received their water from private wells; these wells were tested and found to have low PFAS levels, and therefore all addresses with private wells were also assumed to have had low water contamination levels.

Based on the source of drinking water at their residency, we assigned Ronneby residents to mutually exclusive groups: 'never-high' and 'ever-high'. The 'never-high' group comprised subjects who never lived at an address supplied by the highly contaminated waterworks between 1985 and 2013. The 'ever-high' group comprised subjects who lived at an address supplied by the highly contaminated waterworks for at least some time between 1985 and 2013. During the study period, people could have moved from 'never-high' to 'ever-high', but not the other way around.

We assumed that PFAS levels in drinking water were likely to have been lower in the early stages of the observation period and increased over time. Given the long half-lives of PFAS, we also assumed that the burden of exposure on the body would have increased over time

Table 2
Number of cancer cases in the two different exposure categorizations, the calendar-period approach (never-, early- or late-high) and the total number of years approach (never-, short- or long-high).

	Never-high	Early-high	Late-high	Total
Never-high	4,362	–	–	4,362
Short-high	–	590	121	711
Long-high	–	255	374	629
Total	4,362	845	495	5,702

Table 3
Geometric mean and range of serum levels of PFOS, PFHxS, and PFOA in 3084 persons from Ronneby, sampled 2014–15, and 226 persons from a reference municipality, sampled in 2016.

	N	PFOS (ng/mL)	PFHxS (ng/mL)	PFOA (ng/mL)
Ronneby "never-high" [a]	582	40 (0.58, 839)	30 (0.14, 974)	3.5 (0.04, 49)
Ronneby "ever-high" [b]	2502	199 (0.68, 1868)	176 (0.23, 1658)	11 (0.04, 92)
Ronneby "early-high" [c]	283	48 (4.5, 505)	43 (1.6, 508)	3.6 (0.5, 39)
Ronneby "late-high" [d]	2219	239 (0.68, 1868)	210 (0.23, 1658)	13 (0.04, 92)
Reference [e]	226	3.9 (0.27, 49)	0.84 (0.22, 28)	1.5 (0.22, 4.9)

[a] Never-high consisted of subjects who resided in Ronneby, but never resided in the area with water supply from the highly contaminated waterworks at the home address or had own well in 1985–2013.

[b] Ever-high consisted of subjects who resided in Ronneby, in the area with water supply from the highly contaminated waterworks at home address any time in 1985–2013. Participants from a nearby municipality, Karlshamn, with no elevated PFAS levels in drinking water.

[c] Early-high consisted of subjects who resided in Ronneby, in the area with water supply from the highly contaminated waterworks at home address in 1985–2004, but not later.

[d] Late-high consisted of subjects who resided in Ronneby, in the area with water supply from the highly contaminated waterworks at home address in 2005–2013, may also resided in the same area in 1985–2004.

[e] Reference consisted of subject who resided in neighbouring municipality, Karlshamn. Never resided in Ronneby during 1985–2013.

between 1985 and 2013, and then decreased slowly after the cessation of the external exposure (Li et al., 2018). Therefore, we further subdivided the 'ever-high' group into 'early-high' and 'late-high' groups. A person who, at some time between 1985 and 2004, lived in the Ronneby area supplied with highly contaminated water was classified as 'early-high' from the first year of living in this area. A person who, at some time between 2005 and 2013, lived in the Ronneby area supplied with highly contaminated water was classified as 'late-high' from the first year of living in this area. Thus, a person who lived in the highly contaminated water supply area for the entire study period would shift from 'early-high' to 'late-high' in 2005.

The 'ever-high' group was further subdivided into 'short-high' and 'long-high' groups, according to the length of time a person lived at an address supplied by the contaminated waterworks. People residing in the contaminated supply area for 1–10 years were classified as 'short-high', and those living in the area for 11 years or more as 'long-high'. Notably, the calendar-period approach differs from the approach using the total number of years; the number of cases in 'short-high' and 'early-high' is not the same as the number in the 'long-high' and 'late-high' groups (Table 2).

All three exposure classifications are time varying in a unidirectional manner, as described above. During 2014–2016, an exposed person was classified according to their highest exposure.

The validity of the categorization described above was evaluated and confirmed in a subcohort of participants whose serum PFAS levels were measured during 2014–2015 (Table 3).

2.4. Diagnosis of malignant neoplasm

Information on neoplasm diagnosis was obtained from the nationwide Swedish Cancer Register. Reporting is mandatory for clinicians and for pathology departments, and 99% of reported cases are morphologically defined (Socialstyrelsen, 2019). The Swedish Cancer Register uses the seventh revision of the International Classification of Diseases (ICD-7) as the main code for all sites. We included the first diagnosis of malignant neoplasm for each person. Benign tumours were not included.

The study period was restricted to the period from 1985 (when PFAS contamination of the aquifer, and consequently the drinking water, is assumed to have started) to 2016 (the end of follow-up). Furthermore, participants were censored after age 85, as the chance of not reporting to the Cancer Register increases in elderly patients with advanced stage cancer (Socialstyrelsen, 2019).

2.5. Statistical analysis

Two different statistical approaches were used for the cohort analyses. First, an external comparison was performed by calculating sex, age and calendar year standardized incidence ratios (SIR) for overall and specific cancers, in which the 'never-high' and 'ever-high' groups, respectively, were compared with both a regional and a national external reference population. The regional external reference population was the population of Blekinge County excluding Ronneby municipality, and the national reference population was the whole Swedish population. Thus, this external comparison takes into account the fact that the 'never-high' population from Ronneby was still likely to have had a higher-than-background exposure level (Table 1, Supplementary Table 2). The SIRs and 95% confidence intervals (CI) were calculated by treating the observed number as a Poisson variable, or a normal variable if the observed value was greater than 15. Information on cancer incidence in the reference population was obtained from the National Board of Health and Welfare up to 2014, with extrapolation to 2016.

Next, internal comparisons were performed within the Ronneby Register Cohort, using the 'never-high' group as the reference. The Cox proportional hazard model, with calendar year on the time axis and adjustment for age and sex (where applicable), was used to estimate hazard ratios (HR). This internal comparison was performed for overall cancer and for cancers of which there were $\geq$15 cases in both men and women combined in the cohort. To assess the risk related to any exposure at residence, the 'ever-high' group was compared with the 'never-high' group. Assessment of the risk related to the calendar period of exposure at residence was made by comparing the 'early-high' and 'late-high' groups with the 'never-high' group. To assess the risk related to the total number of exposed years at residence, the 'short-high' and 'long-high' groups were compared with the 'never-high' group.

In the internal comparisons, sensitivity analyses were also performed by adjusting for highest education achieved ('low', up to 9 years of education; 'medium', 10–12 years; 'high', more than 12 years; available for about 80% of the population). To assess whether risk differed between men and women, an interaction term between sex and exposure group was included. Cox modelling was performed using STATA 16 software (StataCorp LLC, USA).

Ethics approval

The study was approved by the Regional Ethical Review Board in Lund, Sweden (approval number: 2014/267 and 2015/902).

Table 4
Characteristics of the study population.

Characteristic	Male		Female	
	Never-high [a]	Ever-high [b]	Never-high [a]	Ever-high [b]
Number of subjects	23,763	8,175	20,933	7,636
Person-years	491,786	151,489	445,191	142,416
Age at entering cohort group (mean ± SD)	31 ± 22 [c]	30 ± 22 [d]	33 ± 24 [c]	31 ± 23 [d]
Highest education				
< 9 years (%)	4,233 (18)	1,841 (23)	3,928 (19)	1,793 (23)
10–12 years (%)	7,383 (31)	3,337 (41)	6,107 (29)	2,855 (37)
>12 years (%)	7,776 (33)	1,631 (20)	6,439 (31)	1,649 (22)
Missing	4,371 (18)	1,366 (17)	4,459 (21)	1,339 (18)

[a] 'Never-high' comprised subjects who resided in Ronneby, but never resided in an area receiving water supply from the highly contaminated waterworks (including those who had a private well) between 1985 and 2013.
[b] 'Ever-high' comprised subjects who resided in Ronneby, at an address supplied by the highly contaminated waterworks, at any time between 1985 and 2013.
[c] Age at entering the cohort.
[d] Age at the first year of registered residence at an address supplied with contaminated drinking water.

3. Results

3.1. Characteristics and exposure

The average ages at entry into the cohort in the 'never-high' group (mean 31 years old for males and 33 years old for females) and at the first year of registered residence at an address with contaminated drinking water in the 'ever-high' group (mean 30 years old for males and 31 years old for females) were similar (Table 4). The level of highest education achieved was not uniform between groups: the 'never-high' group contained a higher proportion of subjects with 'high' education level than the 'ever-high' group did.

In this cohort, we identified 5,702 subjects (3,124 men, 55%; and 2,578 women, 45%) who received a cancer diagnosis between 1985 and 2016. Most (4,950 cases, 87%) were diagnosed in Blekinge County, indicating that the person was still living there at the time of diagnosis.

3.2. External comparisons

The SIRs for overall cancer were at unity or below, and were similar between the 'never-high' and 'ever-high' groups in both men and women. Only cancer types for which there were more than 15 cases were analysed. In the 'ever-high' group versus the 'never-high' group, nominally higher SIR estimates (here defined as >25% difference) were observed for cancers of the rectum, trachea and lung, testicle, kidney, brain, bone and cartilage in men, and for cancers of the rectum, ovary, kidney, bladder and thyroid, as well as for melanoma, in women. In the 'ever-high' group versus the 'never-high' group, nominally lower SIRs estimates (<25%) were observed for non-melanoma skin cancer in women (Table 5). Combined results for males and females were generally similar (Supplementary Table S2).

Similar results were obtained when comparing the study population against the whole Swedish reference population (data not shown).

3.3. Internal comparisons

All internal comparisons confirmed the findings in the external analysis that there was no excess in overall cancer risk in the exposed population (Tables 6–8). For the most prevalent cancers, prostate and breast cancer, the risk estimates in all exposure categories were below or at unity. For several other cancer types, the HR point estimates were modestly increased, but with wide confidence intervals that included unity, showing that the estimates were not precise.

Cancers of the kidney, bladder, brain, bone and cartilage, thyroid and testicle exhibited increased HR estimates in the 'ever-high' group (Table 6), increased HR in the 'late-high' group (higher than in the 'early-high' group, Table 7), and increased HR in the 'long-high' group (higher than in the 'short-high' group, Table 8) (Fig. 1). By contrast, prostate cancer showed decreased HR in the 'ever-high', 'late-high', and 'long-high' groups.

Although the external analysis indicated that men and women had different risks for some cancers, the internal comparison showed that no cancers had an interaction term (exposure × sex) with a low *P*-value (all *P*-values for interaction term were above 0.15; data not shown). Additional adjustment for highest achieved education reduced the sample size because of missing information, but did not change the results (Tables S3, S4, and S5, Supplementary Information).

4. Discussion

In this study, we evaluated the cancer risk in a Swedish municipality with high exposure to various PFAS compounds from firefighting foams via drinking water. The exposure was dominated by PFOS, PFHxS and, to a lesser degree, PFOA. No increased overall risk of cancer was observed. The findings also clearly showed no excess risk for prostate or breast cancer, the most common cancers in men and women, respectively. For several cancer types, the risk estimates indicated modestly increased risks; however, the confidence intervals were wide and included unity.

The PFAS exposure found in Ronneby was extremely high, especially for PFHxS. In a biomonitoring study with ~3300 Ronneby residence participated, it was found that serum PFHxS level in Ronneby population was on average more than 100 times higher than the Swedish general population (Xu et al., 2021), and about 30 times higher than was found in C8 study (Frisbee et al., 2009). For PFOS, it was 35 times and 7 times higher, respectively. PFOA level in Ronneby population was about 1/5 the level in the C8 study, but still was 4.5 times higher than the general population. The high exposure levels and different PFAS composition in Ronneby make the present study a valuable contribution to the existing research regarding PFAS exposure and cancer risk.

4.1. Findings in relation to other studies

Kidney cancer is of concern because previous findings from i) the C8 Science Panel Study of PFOA exposure (Barry et al., 2013; Steenland et al., 2020; Vieira et al., 2013), ii) a recent case-control study with background exposure levels in the US (Shearer et al., 2021), iii) an ecological mortality study in an area of Italy with PFOA contamination (Mastrantonio et al., 2018), and iv) a PFOA occupational cohort mortality study (Steenland and Woskie, 2012) have all reported an association between PFAS exposure and kidney cancer, either overall or in a subgroup of the study population. Most studies investigated the risk in men and women combined, but in their ecological mortality study, Mastrantonio et al. reported a higher risk in women but not for men, nor for both sexes combined (Mastrantonio et al., 2018). The internal comparisons within our cohort, performed using various exposure categorization strategies, consistently indicated a modestly increased risk for kidney cancer, although most CIs were wide and included unity. The internal comparison contrasting late and early exposure in Table 7 showed no risk for the 'early-high' group and a raised HR in the 'late--high' group, compared to the 'never-high' group. The serum measurements (Table 3) suggest that the exposure contrast between the 'never-high' and 'early-high' group is quite small. Thus the pattern is suggestive of an increased risk for kidney cancer in particular. Furthermore, the SIR for kidney cancer was lower in men, but higher in

Table 5
Age- and calendar-year-standardized cancer incidence ratio (SIR) with 95% confidence interval (CI) in Ronneby residents who never or ever lived at an address supplied with highly PFAS-contaminated drinking water. Blekinge County excluding Ronneby is used as the reference population. *N*: number of diagnoses.

Cancer type	Male				Female			
	Never-high [a]		Ever-high [b]		Never-high [a]		Ever-high [b]	
	N	SIR (95% CI)	*N*	SIR (95% CI)	*N*	SIR (95% CI)	*N*	SIR (95% CI)
Overall	2368	1.00 (0.96, 1.05)	725	1.04 (0.96, 1.12)	1949	0.89 (0.85, 0.93)	600	0.89 (0.82, 0.96)
Lip	10	0.74 (0.36, 1.36)	2	0.57 (0.07, 2.05)	2	0.38 (0.05, 1.38)	3	1.96 (0.40, 5.72)
Oral	18	1.05 (0.62, 1.67)	6	1.14 (0.42, 2.49)	10	0.64 (0.31, 1.18)	3	0.59 (0.12, 1.73)
Salivary gland	2	0.47 (0.06, 1.70)	2	1.68 (0.20, 6.06)	3	1.14 (0.23, 3.32)	0	0.00 (0.00, 5.29)
Pharynx	16	0.88 (0.50, 1.43)	8	1.45 (0.63, 2.85)	6	0.92 (0.34, 2.00)	2	0.98 (0.12, 3.53)
Oesophagus	33	1.02 (0.70, 1.44)	7	0.71 (0.29, 1.47)	11	1.03 (0.51, 1.83)	2	0.64 (0.08, 2.31)
Stomach	82	1.00 (0.80, 1.24)	24	1.10 (0.70, 1.64)	37	0.85 (0.60, 1.17)	13	1.03 (0.55, 1.76)
Colon	172	1.01 (0.87, 1.18)	50	0.99 (0.73, 1.30)	156	0.88 (0.75, 1.03)	45	0.84 (0.62, 1.13)
Rectum	109	0.96 (0.79, 1.16)	41	1.25 (0.89, 1.69)	80	1.00 (0.79, 1.24)	32	1.33 (0.91, 1.88)
Liver	24	1.12 (0.72, 1.66)	9	1.52 (0.70, 2.89)	9	0.98 (0.45, 1.86)	4	1.52 (0.41, 3.88)
Gallbladder, bile duct	11	0.56 (0.28, 1.00)	6	1.10 (0.40, 2.40)	32	1.21 (0.83, 1.70)	7	0.99 (0.40, 2.05)
Pancreas	38	0.84 (0.60, 1.16)	6	0.46 (0.17, 1.01)	39	0.93 (0.66, 1.27)	10	0.81 (0.39, 1.50)
Nose, sinuses	6	1.43 (0.52, 3.11)	0	0.00 (0.00, 3.08)	0	0.00 (0.00, 1.80)	0	0.00 (0.00, 5.15)
Larynx	10	0.48 (0.23, 0.89)	4	0.67 (0.18, 1.71)	1	0.43 (0.01, 2.37)	3	4.54 (0.94, 13.3)
Trachea, lung	177	1.11 (0.96, 1.29)	64	1.42 (1.09, 1.81)	100	0.94 (0.76, 1.14)	29	0.88 (0.59, 1.27)
Pleura	12	0.61 (0.32, 1.07)	2	0.35 (0.04, 1.25)	1	0.57 (0.01, 3.19)	1	1.97 (0.05, 11.0)
Breast	2	0.44 (0.05, 1.57)	1	0.74 (0.02, 4.14)	525	0.80 (0.73, 0.87)	156	0.75 (0.64, 0.88)
Cervix	–	–	–	–	55	0.97 (0.73, 1.26)	15	0.81 (0.45, 1.33)
Uterus	–	–	–	–	113	0.94 (0.77, 1.13)	30	0.82 (0.55, 1.17)
Ovarian	–	–	–	–	68	0.87 (0.68, 1.11)	25	1.12 (0.72, 1.65)
Vulva, vagina	–	–	–	–	17	0.80 (0.47, 1.29)	4	0.61 (0.17, 1.57)
Prostate	712	1.14 (1.05, 1.22)	181	0.96 (0.82, 1.11)	–	–	–	–
Testicle	30	0.85 (0.57, 1.21)	14	1.28 (0.70, 2.15)	–	–	–	–
Kidney	46	0.67 (0.49, 0.90)	17	0.86 (0.50, 1.38)	43	1.17 (0.84, 1.57)	16	1.47 (0.84, 2.39)
Bladder	166	0.94 (0.80, 1.09)	57	1.10 (0.84, 1.43)	35	0.69 (0.48, 0.95)	17	1.13 (0.66, 1.80)
Skin (melanoma)	115	1.27 (1.05, 1.53)	34	1.20 (0.83, 1.67)	103	0.96 (0.79, 1.17)	43	1.21 (0.88, 1.63)
Skin (non-melanoma)	135	0.73 (0.61, 0.86)	47	0.85 (0.63, 1.13)	89	0.74 (0.60, 0.91)	20	0.55 (0.34, 0.85)
Brain	56	0.93 (0.70, 1.21)	24	1.29 (0.83, 1.93)	52	0.73 (0.55, 0.96)	18	0.82 (0.49, 1.30)
Thyroid	14	1.33 (0.73, 2.23)	3	0.89 (0.18, 2.61)	32	1.38 (0.94, 1.95)	16	2.08 (1.19, 3.38)
Bone, cartilage	22	1.35 (0.85, 2.04)	11	2.34 (1.17, 4.20)	17	1.01 (0.59, 1.62)	4	0.76 (0.21, 1.95)
Non-Hodgkin	87	1.00 (0.80, 1.23)	26	0.97 (0.63, 1.41)	62	0.99 (0.76, 1.27)	15	0.78 (0.44, 1.29)
Mb Hodgkin's	13	1.34 (0.71, 2.29)	3	1.06 (0.22, 3.11)	10	1.35 (0.65, 2.48)	4	1.75 (0.48, 4.48)
Myeloma	39	1.02 (0.72, 1.39)	11	0.94 (0.47, 1.69)	30	0.93 (0.63, 1.33)	9	0.91 (0.42, 1.73)
Chronic lymphocytic leukaemia	35	1.33 (0.92, 1.85)	9	1.24 (0.57, 2.35)	17	1.10 (0.64, 1.77)	4	0.88 (0.24, 2.25)
Chronic myelogenous leukaemia	7	1.72 (0.69, 3.54)	3	2.56 (0.53, 7.47)	4	0.95 (0.26, 2.43)	2	1.71 (0.21, 6.19)
Polycythaemia vera	6	1.05 (0.38, 2.27)	3	1.72 (0.35, 5.02)	5	1.66 (0.54, 3.88)	1	1.11 (0.03, 6.20)

[a] 'Never-high' comprises subjects who resided in Ronneby, but never resided at an address supplied by the highly contaminated waterworks (including those who had a private well) between 1985 and 2013.
[b] 'Ever-high' comprises subjects who resided in Ronneby, at an address supplied by the highly contaminated waterworks, at any time between 1985 and 2013.

women, in the cohort than in the county reference population, suggesting that the study cohort may differ from the external reference population. However, the increases in relation to PFAS exposure is present for both men and women. Taking these results together, the consistent pattern by exposure categories in our cohort provides some additional evidence for an elevated risk of kidney cancer related to PFAS exposure even for exposures dominated by PFOS and PFHxS.

For testicular cancer, an association with PFOA exposure was reported by the C8 Science Panel Study (Barry et al., 2013). We observed a moderately increased risk estimate for testicular cancer in the 'ever--high' category, but no marked contrasts in further internal exposure subcategories. All CIs were wide and included unity. The results of our study, based on 44 cases, provide some weak additional support for an association with PFAS exposure, but the overall evidence remains scarce.

Findings in the C8 Science Panel Study, especially among occupationally exposed workers, gave some support for an association between PFOA exposure and thyroid cancer (Barry et al., 2013). As in our study, there were few cases among men. In our external comparisons, we observed increased SIR for thyroid cancer in women, and modestly increased HRs in all exposure categories in the internal comparisons (men and women combined), but CIs included unity. Overall, there is some support for an association, but the evidence remains limited.

Studies performed in an occupational cohort in a 3 M manufacturing plant in Decatur reported an increased standardized mortality ratio (Alexander et al., 2003) but no increased standardized incidence ratio (Alexander and Olsen, 2007) for bladder cancer in relation to PFOS exposure. No increased risk of bladder cancer was observed in the C8 Science Panel Study (Barry et al., 2013; Steenland et al., 2020; Vieira et al., 2013). A previous study in the general population with

Table 6
Internal comparisons of cancer risk between groups with respect to exposure to PFAS-contaminated drinking water at their home. The results are presented as hazard ratio (HR) from Cox proportional hazard model. All analyses were adjusted for age and sex.

Cancer	Never-high [a]	Ever-high [b]		
	N	*N*	HR	95% CI
Overall	4,320	1,325	1.02	0.96, 1.09
Stomach	119	37	1.14	0.79, 1.66
Colon	326	93	0.98	0.78, 1.23
Rectum	190	73	1.25	0.95, 1.64
Gall bladder, bile duct	43	13	1.15	0.62, 2.15
Pancreas	77	16	0.71	0.41, 1.22
Trachea, lung	277	93	1.14	0.9, 1.45
Breast [c]	525	156	0.95	0.79, 1.13
Cervix [c]	55	15	0.91	0.51, 1.61
Uterus [c]	113	31	0.9	0.6, 1.34
Ovarian [c]	68	25	1.24	0.78, 1.96
Prostate [c]	712	181	0.83	0.71, 0.98
Testicle [c]	31	14	1.38	0.73, 2.61
Kidney	89	33	1.27	0.85, 1.91
Bladder	200	74	1.30	0.99, 1.69
Skin (melanoma)	218	77	1.09	0.84, 1.41
Skin (non-melanoma)	225	67	0.99	0.75, 1.3
Brain	109	42	1.24	0.86, 1.77
Thyroid	46	19	1.36	0.79, 2.33
Bone, cartilage	39	15	1.33	0.73, 2.42
Non-Hodgkin	149	41	0.94	0.67, 1.34
Myeloma	69	20	0.95	0.58, 1.57
Chronic lymphocytic leukaemia	52	13	0.84	0.46, 1.54

[a] 'Never-high' comprises subjects who resided in Ronneby, but never resided at an address supplied by the highly contaminated waterworks (including those who had their own well) between 1985 and 2013.
[b] 'Ever-high' comprises subjects who resided in Ronneby, at an address supplied by the highly contaminated waterworks, at any time between 1985 and 2013.
[c] Analyses were limited to the relevant sex.

Table 7
Internal comparisons of cancer risk among groups in terms of PFAS exposure and time period. The results were obtained from Cox proportional hazard model. All analyses were adjusted for age and sex.

Cancer	Never-high [a]	Early-high [b]			Late-high [c]		
	N	*N*	HR	95% CI	*N*	HR	95% CI
Overall	4,320	832	0.99	0.91, 1.06	493	1.09	0.99, 1.20
Stomach	119	26	1.13	0.73, 1.73	11	1.18	0.61, 2.28
Colon	326	60	0.96	0.73, 1.27	33	1.02	0.70, 1.48
Rectum	190	50	1.30	0.95, 1.78	23	1.15	0.73, 1.82
Gallbladder, bile duct	43	10	1.12	0.56, 2.25	3	1.26	0.36, 4.42
Pancreas	77	12	0.90	0.49, 1.66	4	0.43	0.15, 1.19
Trachea, lung	277	55	1.05	0.79, 1.41	38	1.32	0.92, 1.88
Breast [d]	525	102	0.94	0.76, 1.16	54	0.96	0.72, 1.29
Cervix [d]	55	11	0.92	0.48, 1.77	4	0.85	0.30, 2.42
Uterus [d]	113	16	0.71	0.42, 1.20	15	1.27	0.72, 2.26
Ovarian [d]	68	23	1.53	0.95, 2.46	2	0.37	0.09, 1.56
Prostate [d]	712	114	0.88	0.72, 1.08	67	0.76	0.59, 0.98
Testicle [d]	31	9	1.35	0.64, 2.84	5	1.46	0.55, 3.83
Kidney	89	19	1.05	0.64, 1.73	14	1.85	1.00, 3.40
Bladder	200	46	1.20	0.87, 1.66	28	1.50	0.98, 2.29
Skin (melanoma)	218	36	0.82	0.58, 1.17	41	1.54	1.09, 2.19
Skin (non-melanoma)	225	35	0.89	0.62, 1.28	32	1.13	0.76, 1.66
Brain	109	26	1.20	0.78, 1.84	16	1.31	0.76, 2.26
Thyroid	46	11	1.20	0.62, 2.33	8	1.69	0.77, 3.73
Bone, cartilage	39	10	1.18	0.59, 2.37	5	1.81	0.68, 4.83
Non-Hodgkin	149	25	0.83	0.54, 1.27	16	1.22	0.71, 2.10
Myeloma	69	10	0.74	0.38, 1.45	10	1.36	0.67, 2.76
Chronic lymphocytic leukaemia	52	8	0.73	0.34, 1.54	5	1.13	0.43, 2.99

[a] 'Never-high' comprises subjects who resided in Ronneby, but who never resided at an address supplied by the highly contaminated waterworks (including those who had their own well) between 1985 and 2013.
[b] 'Early-high' comprises subjects who resided in Ronneby, and who lived at an address supplied by the highly contaminated waterworks between 1985 and 2004 but not later.
[c] 'Late-high' comprises subjects who resided in Ronneby, and who lived at an address supplied by the highly contaminated waterworks between 2005 and 2013. Subjects may have also resided in the same area between 1985 and 2004.
a, b, c. 'Early-high' and 'late-high' were the subdivision of 'ever-high'.
[d] Analyses were limited to the relevant sex.

background exposures did not find an association between PFOA, PFOS and bladder cancer (Eriksen et al., 2009). In our external comparison, SIRs for bladder cancer were slightly higher in the 'ever-high' than in the 'never-high' categories for both men and women, reaching statistical significance in the internal analysis. The lack of information about smoking status and occupation in our cohort is a clear limitation. Even though adjustment for educational level did not alter the results, there may still be unmeasured confounding factors.

For lung cancer, the external analysis showed increased SIRs in men in the 'ever-high' category, but no increase among women. The internal analysis showed a lower HR estimate for the 'long-high' than the 'short-high' category. No increased risk for lung cancer was reported from the C8 Science Panel Study. The lack of information about smoking status and occupation may also be an important limitation here.

Moderately increased SIRs for rectum cancer were found in the 'ever-high' group in both men and women, while the estimates for colon cancer were below or at unity. In the internal comparisons, HR estimates exceeded unity for rectal cancer in the 'ever-high' category and its subgroups. The C8 Science Panel Study found no association between colon-rectal cancer and PFOA exposure (Barry et al., 2013; Vieira et al., 2013), and a cross-sectional study using the same study population showed a strong inverse association between prior colorectal cancer and PFOS and PFOA measured subsequently (Innes et al., 2014). Further studies, separating colon and rectal cancer, are clearly warranted.

Unexpectedly, our external analysis indicated increased SIRs for melanoma, especially in women. The internal analysis indicated highest HR in the 'late-high' category, with less contrast between 'short-high' and 'long-high' categories. An increased risk of melanomas related to PFAS exposure has not previously been reported.

Likewise, we found unexpected signals for bone and cartilage cancer, especially among men, with highest HR in the 'late-high' and 'long-high' categories. We are unaware of any similar data from other studies, and the observations should be viewed with caution.

Previous studies on PFAS and breast cancer have showed inconsistent results; most studies at background exposure levels found no association (Bonefeld-Jorgensen et al., 2011, 2014; Hurley et al., 2018; Mancini et al., 2020; Tsai et al., 2020). Similarly, no increased risk was found in the C8 Science Panel Study (Barry et al., 2013; Vieira et al.,

Table 8
Internal comparisons of cancer risk among groups of people who resided at an address supplied with water from the highly contaminated waterworks for short or long periods of time. The results were obtained from Cox proportional hazard model. All analyses were adjusted for age and sex.

Cancer	Never-high [a]	Short-high [b]			Long-high [c]		
	N	*N*	HR	95% CI	*N*	HR	95% CI
Overall	4,320	704	1.03	0.95, 1.11	621	1.02	0.93, 1.11
Stomach	119	16	0.86	0.51, 1.46	21	1.56	0.95, 2.55
Colon	326	51	1.02	0.76, 1.37	42	0.93	0.67, 1.30
Rectum	190	33	1.16	0.80, 1.69	40	1.34	0.94, 1.90
Gallbladder, bile duct	43	7	0.98	0.44, 2.20	6	1.46	0.59, 3.61
Pancreas	77	11	0.89	0.47, 1.67	5	0.49	0.19, 1.22
Trachea, lung	277	52	1.23	0.92, 1.66	41	1.04	0.74, 1.46
Breast [d]	525	89	1.01	0.80, 1.26	67	0.87	0.67, 1.13
Cervix [d]	55	13	1.09	0.60, 2.01	2	0.42	0.10, 1.75
Uterus [d]	113	13	0.73	0.41, 1.30	18	1.09	0.65, 1.81
Ovarian [d]	68	18	1.52	0.90, 2.57	7	0.82	0.37, 1.82
Prostate [d]	712	95	0.96	0.78, 1.20	86	0.72	0.58, 0.91
Testicle [d]	31	9	1.32	0.63, 2.79	5	1.51	0.56, 4.03
Kidney	89	15	1.11	0.64, 1.92	18	1.47	0.87, 2.49
Bladder	200	39	1.23	0.87, 1.73	35	1.39	0.95, 2.02
Skin (melanoma)	218	40	1.04	0.74, 1.46	37	1.14	0.80, 1.64
Skin (non-melanoma)	225	23	0.71	0.46, 1.10	44	1.25	0.89, 1.75
Brain	109	21	1.06	0.66, 1.69	21	1.50	0.92, 2.44
Thyroid	46	12	1.35	0.71, 2.56	7	1.38	0.60, 3.18
Bone, cartilage	39	7	0.95	0.42, 2.13	8	2.12	0.94, 4.76
Non-Hodgkin	149	20	0.78	0.49, 1.25	21	1.19	0.74, 1.91
Myeloma	69	13	1.25	0.69, 2.27	7	0.66	0.30, 1.45
Chronic lymphocytic leukaemia	52	9	1.12	0.55, 2.28	4	0.53	0.19, 1.49

[a] 'Never-high' comprises subjects who resided in Ronneby, but who never resided at an address supplied by the highly contaminated waterworks (including those who had their own well) between 1985 and 2013.
[b] 'Short-high' comprises subjects who resided in Ronneby, and who lived at an address supplied with water by the highly contaminated waterworks for 1–10 years.
[c] 'Long-high' comprises subjects who resided in Ronneby, and who lived at an address supplied with water by the highly contaminated waterworks for 11 years or more. a, b, c. 'Short-high' and 'long-high' were the subdivision of 'ever-high'.
[d] Analyses were limited to the relevant sex.

2013). Our findings, with risk estimates below unity, are in agreement with these earlier results.

Although there are indications that PFAS might affect the function of the ovary (Ding et al., 2020), the relationship between PFAS exposure and ovarian cancer has been little studied. As in the C8 Science Panel Study, we found no consistent pattern of relationship between exposure and ovarian cancer (Barry et al., 2013; Vieira et al., 2013).

A statistically significant decreased risk for prostate cancer was observed in the 'ever-high' category of our study. No association between prostate cancer and PFOA exposure was observed in the C8 Science Panel Study (Barry et al., 2013; Vieira et al., 2013). Two studies in populations at background PFAS exposure levels have investigated the risk for prostate cancer, and no associations were found (Eriksen et al., 2009; Hardell et al., 2014). A study in an occupational cohort in the 3 M Minnesota PFOA manufacturing plant did not find an association between ammonium perfluorooctanoate and prostate cancer (Raleigh et al., 2014). Since our result seems to contradict previous reports, it should be interpreted with extra caution.

Two studies had fed rats with PFAS in food for two years. Carcinogenic changes were found in testicle, liver, and pancreas, but mostly in the group exposed to the high dose (Biegel et al., 2001; Butenhoff et al., 2012; Caverly Rae et al., 2014). The findings showed clearly that PFAS exposures induce tumours in rats. However, whether or not these effects are relevant to humans is difficult to ascertain. Therefore, direct human evidence is critically important for evaluating the cancer risk to humans induced by PFAS exposure.

4.2. Strengths and limitations

The strength of our study is the unbiased inclusion and excellent follow-up, based on personal ID, a national population register and a cancer register with dual reporting from clinicians and pathology departments. The exposure assessment based on annual residence addresses, coupled with information on drinking water supply, is free from retrospective self-reporting bias, but allows only a crude estimate of ingested PFAS. Still, fair validity was confirmed by comparisons with serum levels in a subcohort. The lack of information on important covariates such as smoking habits, body mass index and occupational exposure is a limitation. However, the highest achieved educational level was used for adjustment, as a surrogate of socioeconomic status, and it also correlates well with smoking behaviour (Eek et al., 2010). The fact that adjustment for highest achieved education did not substantially change the results indicates that our findings here are probably not purely due to confounding by smoking.

The present study used both internal and external comparisons to investigate the associations between PFAS and cancer risk. The rationale for including an external comparison was that no residents of Ronneby were expected to be truly unexposed to PFAS-contaminated drinking water. In fact, people who had always resided in the area with uncontaminated water in Ronneby (i.e., those representing the 'never-high' group) showed higher serum PFAS levels than people from a reference municipality with PFAS levels similar to the general Swedish population (Li et al., 2018; Xu et al., 2021). SIRs from the external comparisons could thus be viewed as ecological comparisons, separating three areas with different external PFAS exposure levels.

5. Conclusion

This is the first report on cancer risk in populations with high PFAS exposure emanating from firefighting foams. Our study reveals no evidence of an overall excess risk of cancer in the population, and no increased risks for the most common cancer types, such as prostate and breast. Combining evidence from this study with that from previous studies strengthens the overall evidence for a modestly increased association between PFAS exposure and kidney cancer, and possibly also thyroid and testicular cancer after high exposure to PFAS. Other findings suggesting increased risks, such as for bladder, bone and cartilage cancer and melanomas, merit further investigations. However, these results were unexpected and should be viewed with caution, given the large number of analyses.

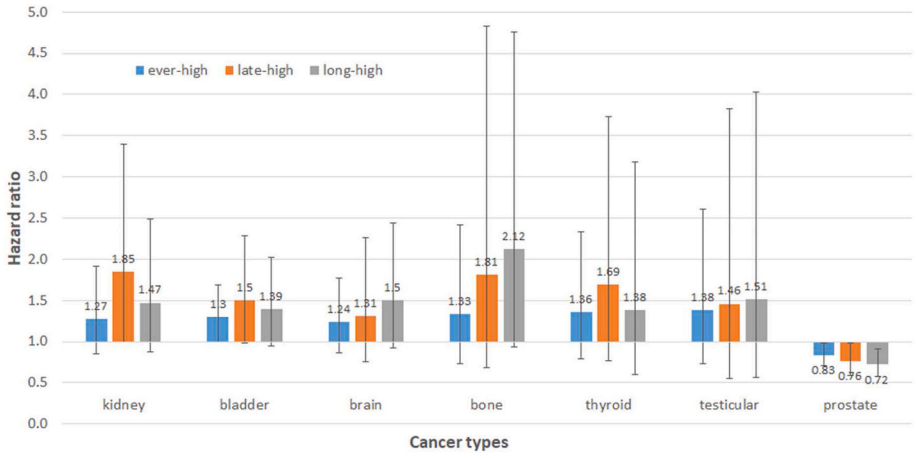

Fig. 1. Hazard ratios and 95% CIs of the cancer types that exhibited the effect of the same direction (increase/decrease) in the 'ever-high', 'late-high', and 'long-high' groups compared with the 'never-high' group.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.112217.

References

Alexander, B.H., Olsen, G.W., 2007. Bladder cancer in perfluorooctanesulfonyl fluoride manufacturing workers. Ann. Epidemiol. 17, 471–478. https://doi.org/10.1016/j.annepidem.2007.01.036.

Alexander, B.H., Olsen, G.W., Burris, J.M., et al., 2003. Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. Occup. Environ. Med. 60, 722–729. https://doi.org/10.1136/oem.60.10.722.

Barry, V., Winquist, A., Steenland, K., 2013. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ. Health Perspect. 121, 1313–1318. https://doi.org/10.1289/ehp.1306615.

Bartell, S.M., Vieira, V.M., 2021. Critical review on PFOA, kidney cancer, and testicular cancer. J. Air Waste Manag. Assoc. 71, 663–679. https://doi.org/10.1080/10962247.2021.1909668.

Benbrahim-Tallaa, L., Lauby-Secretan, B., Loomis, D., et al., 2014. Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone. Lancet Oncol. 15, 924–925. https://doi.org/10.1016/s1470-2045(14)70316-x.

Biegel, L.B., Hurtt, M.E., Frame, S.R., et al., 2001. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. Toxicol. Sci. 60, 44–55. https://doi.org/10.1093/toxsci/60.1.44.

Bonefeld-Jorgensen, E.C., Long, M., Bossi, R., et al., 2011. Perfluorinated compounds are related to breast cancer risk in Greenlandic Inuit: a case control study. Environ. Health 10, 88. https://doi.org/10.1186/1476-069X-10-88.

Bonefeld-Jorgensen, E.C., Long, M., Fredslund, S.O., et al., 2014. Breast cancer risk after exposure to perfluorinated compounds in Danish women: a case-control study nested in the Danish National Birth Cohort. Cancer Causes Control 25, 1439–1448. https://doi.org/10.1007/s10552-014-0446-7.

Butenhoff, J.L., Kennedy Jr., G.L., Chang, S.C., et al., 2012. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. Toxicology 298, 1–13. https://doi.org/10.1016/j.tox.2012.04.001.

Caverly Rae, J.M., Frame, S.R., Kennedy, G.L., et al., 2014. Pathology review of proliferative lesions of the exocrine pancreas in two chronic feeding studies in rats with ammonium perfluorooctanoate. Toxicol Rep 1, 85–91. https://doi.org/10.1016/j.toxrep.2014.04.005.

Ding, N., Harlow, S.D., Randolph Jr., J.F., et al., 2020. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and their effects on the ovary. Hum. Reprod. Update 26, 724–752. https://doi.org/10.1093/humupd/dmaa018.

Eek, F., Ostergren, P.O., Diderichsen, F., et al., 2010. Differences in socioeconomic and gender inequalities in tobacco smoking in Denmark and Sweden; a cross sectional comparison of the equity effect of different public health policies. BMC Publ. Health 10, 9. https://doi.org/10.1186/1471-2458-10-9.

Eriksen, K.T., Sorensen, M., McLaughlin, J.K., et al., 2009. Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. J. Natl. Cancer Inst. 101, 605–609. https://doi.org/10.1093/jnci/djp041.

Frisbee, S.J., Brooks Jr., A.P., Maher, A., et al., 2009. The C8 health project: design, methods, and participants. Environ. Health Perspect. 117, 1873–1882. https://doi.org/10.1289/ehp.0800379.

Guelfo, J.L., Adamson, D.T., 2018. Evaluation of a national data set for insights into sources, composition, and concentrations of per- and polyfluoroalkyl substances (PFASs) in U.S. drinking water. Environ. Pollut. 236, 505–513. https://doi.org/10.1016/j.envpol.2018.01.066.

Hardell, E., Karrman, A., van Bavel, B., et al., 2014. Case-control study on perfluorinated alkyl acids (PFAAs) and the risk of prostate cancer. Environ. Int. 63, 35–39. https://doi.org/10.1016/j.envint.2013.10.005.

Hu, X.C., Tokranov, A.K., Liddie, J., et al., 2019. Tap water contributions to plasma concentrations of poly- and perfluoroalkyl substances (PFAS) in a nationwide prospective cohort of U.S. Women. Environ. Health Perspect. 127, 67006. https://doi.org/10.1289/EHP4093.

Hurley, S., Goldberg, D., Wang, M., et al., 2018. Breast cancer risk and serum levels of per- and poly-fluoroalkyl substances: a case-control study nested in the California Teachers Study. Environ. Health 17, 83. https://doi.org/10.1186/s12940-018-0426-6.

Innes, K.E., Wimsatt, J.H., Frisbee, S., et al., 2014. Inverse association of colorectal cancer prevalence to serum levels of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in a large Appalachian population. BMC Cancer 14, 45. https://doi.org/10.1186/1471-2407-14-45.

EFSA, Knutsen, H.K., Alexander, J., et al., 2018. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. EFSA. J. 16, e05194 https://doi.org/10.2903/j.efsa.2018.5194.

Li, Y., Fletcher, T., Mucs, D., et al., 2018. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup. Environ. Med. 75, 46–51. https://doi.org/10.1136/oemed-2017-104651.

Mancini, F.R., Cano-Sancho, G., Gambaretti, J., et al., 2020. Perfluorinated alkylated substances serum concentration and breast cancer risk: evidence from a nested case-control study in the French E3N cohort. Int. J. Cancer 146, 917–928. https://doi.org/10.1002/ijc.32357.

Raleigh, K.K., Alexander, B.H., Olsen, G.W., et al., 2014. Mortality and cancer incidence in ammonium perfluorooctanoate production workers. Occup. Environ. Med. 71, 500–506. https://doi.org/10.1136/oemed-2014-102109.

EFSA, Schrenk, D., Bignami, M., et al., 2020. Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA. J. 18, e06223 https://doi.org/10.2903/j.efsa.2020.6223.

Shearer, J.J., Callahan, C.L., Calafat, A.M., et al., 2021. Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma. J. Natl. Cancer Inst. 113, 580–587. https://doi.org/10.1093/jnci/djaa143.

Socialstyrelsen, 2019a. Cancerregistret. https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/cancerregistret/. (Accessed 13 May 2021). accessed.

Socialstyrelsen, 2019b. Bortfall Och Kvalitet Om Cancerregistret. https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/cancerregistret/bortfall-och-kvalitet/. (Accessed 15 August 2021). accessed.

Steenland, K., Winquist, A., 2021. PFAS and cancer, a scoping review of the epidemiologic evidence. Environ. Res. 194, 110690. https://doi.org/10.1016/j.envres.2020.110690.

Steenland, K., Woskie, S., 2012. Cohort mortality study of workers exposed to perfluorooctanoic acid. Am. J. Epidemiol. 176, 909–917. https://doi.org/10.1093/aje/kws171.

Steenland, K., Fletcher, T., Stein, C.R., et al., 2020. Review: evolution of evidence on PFOA and health following the assessments of the C8 Science Panel. Environ. Int. 145, 106125. https://doi.org/10.1016/j.envint.2020.106125.

Tsai, M.S., Chang, S.H., Kuo, W.H., et al., 2020. A case-control study of perfluoroalkyl substances and the risk of breast cancer in Taiwanese women. Environ. Int. 142, 105850. https://doi.org/10.1016/j.envint.2020.105850.

Vieira, V.M., Hoffman, K., Shin, H.M., et al., 2013. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. Environ. Health Perspect. 121, 318–323. https://doi.org/10.1289/ehp.1205829.

Xu, Y., Nielsen, C., Li, Y., et al., 2021. Serum perfluoroalkyl substances in residents following long-term drinking water contamination from firefighting foam in Ronneby, Sweden. Environ. Int. 147, 106333. https://doi.org/10.1016/j.envint.2020.106333.